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NON-AQUEOUS TITRIMETRIC ASSAY OF GABAPENTIN IN CAPSULES USING PERCHLORIC ACID AS TITRANT

Two simple, rapid, accurate and inexpensive methods using visual and potentiometric titrimetric techniques are described for the determination of gabapentin (GBP) in bulk drug as well as in capsules. The methods are based on the neutralization reaction of the primary amino group of GBP with acetous perchloric acid as titrant in anhydrous acetic acid medium. The end point was detected either visually using crystal violet as indicator or potentiometrically using a modified glass electrode SCE electrode system. Both methods are applicable over the range 1.0-16.0 mg of GBP and the titration reaction follows a 1:1 stoichiometry. The methods were successfully applied to the determination of GBP in capsules. The validity of the proposed methods was further ascertained by parallel determination by a reference method and by recovery studies via standard-addition technique.

Key words: gabapentin assay; titrimetry; potentiometry; capsules.

Gabapentin (GBP), chemically known as 1-(aminomethyl)cyclohexaneacetic acid [1], is an antiepileptic drug related to γ-butyric acid. Gabapentin crosses the blood brain barrier and is employed for the treatment of partial seizures. Gabapentin has demonstrated analgesic effects in patients with chronic neuropathic pain states [2]. Several analytical methods have been reported for the determination of gabapentin in pharmaceutical preparations such as high performance liquid chromatography (HPLC) [3-8], capillary electrophoresis [9,10], chemiluminometry [11], potentiometry [2], voltammetry [12], spectrofluorimetry [13,14], spectrophotometry [15-20], automated spectrophotometry using piezoelectric pumping [21] and fluorimetry using sequential injection [22].

To the best of our knowledge, no titrimetric method has ever been reported for the determination of GBP in pharmaceuticals. The previously reported methods are applicable only over the microgram level, however, they are sensitive, most of them are time consuming, require multistage procedures, long reaction time for colour development and require expensive instrumental setup. The non-aqueous titrations have become of considerable importance in pharmaceutical analysis and have been accepted by the majority of modern pharmacopoeias as an official analytical method such as British pharmacopoeia (2009) [23]. In addition, the non-aqueous titration technique is very simple and easily adoptable to determine the GBP content in milligram level in the quality control laboratories across the developing countries where modern and expensive instruments are not available.

The present work describes two simple and accurate titrimetric procedures for the determination of GBP in pure drug as well as in capsules. The methods involve the titration of acetous solution of GBP with acetous perchloric acid in acetic acid medium and the end point being detected either visually using crystal violet as indicator or potentiometrically using combined glass electrode.

EXPERIMENTAL

Apparatus

An Elico 120 digital pH meter provided with a combined glass-SCE electrode system (Equip-Tronics, Mumbai, India) was used for potentiometric titration. The salt bridge was filled with saturated solution of potassium chloride in glacial acetic acid.

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Materials and reagents

Pharmaceutical grade gabapentin (GBP) which is reported to be 99.5% pure with a lot No. (G11010609) was received from Sun Pharmaceuticals, Mumbai, India. The following pharmaceutical preparations were purchased from commercial sources in the local market and subjected to analysis: Gabantin-100 (100 mg GBP per capsule) from Sun Pharma Sikkim, Ranipool, East Sikkim, India and Gabapin-300 (300 mg GBP per capsule) from Intas Pharmaceuticals, Dehradun, India.

All chemicals used were of analytical-reagent grade and the solutions were prepared as follows.

Perchloric acid (0.01 M): the commercially available 0.1 M perchloric acid (Merck, Mumbai, India) was appropriately diluted with the glacial acetic acid (Merck, Mumbai, India, sp.gr. 1.05) to get 0.01 M perchloric acid and it was standardized against 0.01 M potassium dihydrogen phthalate [24].

Crystal violet indicator: a 0.2 % crystal violet (Qualigens Fine Chemicals, Mumbai, India, 85.0% dye content) indicator was prepared by dissolving 58.8 mg of the dye in 25 ml of glacial acetic acid.

Preparation of standard GBP solution: a stock standard solution containing 2.0 mg ml^{-1} GBP was prepared by dissolving accurately weighed 200 mg of pure GBP in glacial acetic acid and diluted to the mark in a 100 ml calibrated flask with the same acid.

Assay procedures

Visual titration

Different volumes (0.5-8.0 ml) of standard solution containing 2.0 mg ml^{-1} GBP were taken in a 100 ml dry titration flask and the volume was made up to 10 ml with glacial acetic acid. Two drops of 0.2 % crystal violet indicator were added and the solution was titrated with standard solution of 0.01 M perchloric acid to a pure blue end point. A blank titration was performed in the same manner without drug, and the necessary corrections were made.

Potentiometric titration

An aliquot of the standard drug solution containing 1.0-16.0 mg of GBP was transferred into a 50 ml dry beaker and the solution was diluted to 25 ml by adding glacial acetic acid. A modified glass-saturated calomel electrode was dipped in the solution; the content was stirred magnetically and titrated with 0.01 M $HClO_4$ from a micro burette. Near the equivalence point, the titrant was added in 0.05 ml increments and after each addition of titrant, the solution was stirred for 30 s and the steady potential was recorded. The titration was continued until there was no significant change in the potential on further addition of the titrant. The equivalence point was determined by applying the graphical method using first derivative plot (Figure 1).

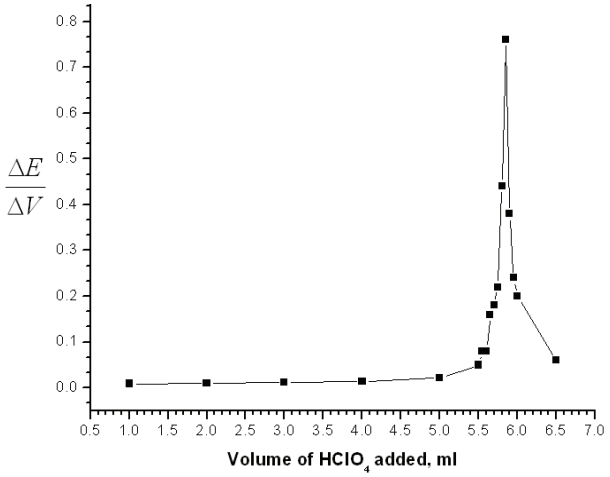


Figure 1. First derivative potentiometric titration curve for the titration of 10 mg of GBP with 0.01 M $HClO_4$.

In both methods, the amount of GBP in the measured aliquot was computed from the following formula:

$$\text{Amount(mg)}=\frac{V\times Mw\times S}{n}$$

where V = ml of the perchloric acid reacted, Mw = relative molecular mass of GBP, S = molarity of perchloric acid and n = number of moles of perchloric acid reacting with each mole of GBP.

Assay procedure for capsules

The content of ten capsules each containing 100 or 300 mg of GBP were weighed. An accurately weighed quantity equivalent to 200 mg of GBP was transferred into a 100 ml calibrated flask and dissolved in 60 ml glacial acetic acid. The contents of the flask were shaken for 15 min; the volume was diluted to the mark with the same acid, mixed well and filtered using a Whatman No. 42 filter paper. The first 10 ml portion of the filtrate was discarded and a suitable aliquot of the filtrate (2.0 mg ml^{-1} GBP) was subjected to analysis following the procedures described for both methods.

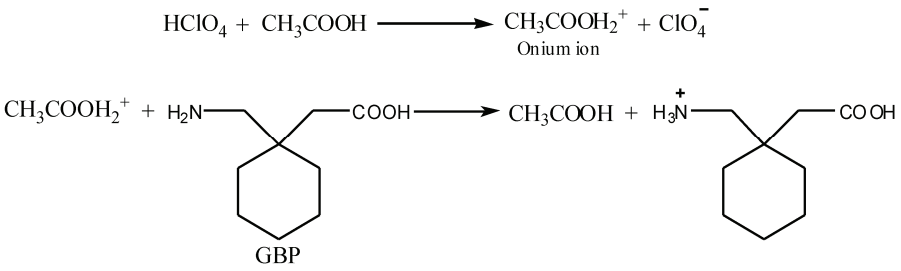
RESULTS AND DISCUSSION

Non-aqueous titrations are widely used in the British Pharmacopoeia, Volumes I and II, for the assay of many drug substances based on the properties of the drug which is either weakly acidic or weak bases [25]. The proposed methods are based on the neutralization reaction of the primary amino group of

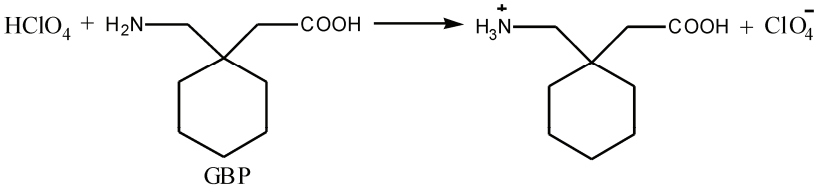
the weak base gabapentin with perchloric acid as a titrant in glacial acetic acid medium. The acetic acid is mostly employed as a solvent for such type of titration due to its protophillic and protogenic properties, and its ability to donate protons and accept protons [26] as follows:

$CH_3COOH \leftrightarrows H^+ + CH_3OO^-$

When a strong acid, such as perchloric acid, is dissolved in a weaker acid, such as acetic acid, the acetic acid is forced to act as a base and accept a proton from the perchloric acid forming an onium ion [25]. The formed onium ion ($CH_3COOH_2^+$) can very readily give up its proton to react with GBP, so basic property of the drug is enhanced and hence, titration between GBP and perchloric acid can often be accurately carried out using acetic acid as solvent. The reactions occurring are as follows:



Overall, the reaction is:



The detection of the end point in the visual method was done by using crystal violet as indicator and the colour change from violet to pure blue being taken as the end point. Also, the detection of the end point in the potentiometric method was accomplished by using combined glass electrode and the end point was taken at the sudden jump in the potential. The reaction stoichiometry was found to be 1:1 (GBP:$HClO_4$) in the range studied (1.0-16.0 mg GBP) for both methods and this ratio was served as the basis for the calculations.

Method validation

The method validation was done according to the present ICH guidelines [27].

Accuracy and precision

The precision of the methods was calculated in terms of intermediate precision (intra-day and inter-day) [28]. Three different amounts of GBP were analysed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision). The percentage relative standard deviation (*RSD*, %) values were ≤1.14% (intra-day) and ≤1.34% (inter-day) indicating high precision of the methods. Also, the accuracy of the methods was evaluated as percentage relative error (*RE*, %) and from the results shown in Table 1, it is clear that the accuracy is satisfactory (*RE* ≤ 1.47%).

Selectivity

To determine the selectivity of the methods, the analytical placebo blank was prepared and subjected to analysis by the proposed methods. It was confirmed that the change in the titre value with respect to the acetic acid blank was caused only by the analyte. To identify the interference by common formulations excipients, a synthetic mixture with the composition: GBP (500 mg), talc (100 mg), corn starch (200 mg), calcium gluconate (100 mg), lactose (250 mg), sodium alginate (50 mg) and magnesium stearate (30 mg), was prepared and subjected to analysis by the proposed methods after solution preparation following the procedure described for capsules. The percent recoveries of GBP were 102.81±1.04 (n = 5) and 101.90±1.63 (n = 5) by visual method and potentiometric method, respectively, suggesting no interference by the excipients in the assay of GBP under the described conditions.

Table 1. Evaluation of intra-day and inter-day precision and accuracy

Method	GBP taken, mg	Intra-day (n = 7)			Inter-day (n = 5)		
		GBP found[a], mg	*RSD*[b] / %	*RE*[c] / %	GBP found[a], mg	*RSD*[b] / %	*RE*[c] / %
Visual method	4.00	3.97	1.07	0.75	3.96	1.26	1.00
	8.00	7.90	0.62	1.25	7.93	0.79	0.88
	12.00	11.88	0.90	1.00	11.90	1.02	0.83
Potentiometric method	5.00	5.06	1.14	1.20	5.05	1.34	1.00
	10.00	10.07	0.93	0.70	10.09	1.02	0.90
	15.00	15.22	1.08	1.47	15.17	1.22	1.13

[a]Mean value of n determinations; [b]relative standard deviation; [c]bias: ((found - taken) / taken)×100.

Application to the assay of capsules

The proposed methods were successfully applied to the determination of GBP in capsules (Table 2). The results obtained were statistically compared with those of the reference method [15] by applying the Student's t-test for accuracy and F-test for precision. The reference method consisted of the measurement of the absorbance of the aqueous extract of the capsules at 210 nm. In all the cases, the average results obtained by the proposed methods and reference method were statistically identical, as the difference between the average values had no significance at 95 % confidence level with respect to accuracy and precision.

Recovery study

To ascertain the validity of the proposed methods, a recovery experiment was performed via standard addition technique. To a fixed and known amount of drug in capsule powder (pre-analyzed), pure drug was added at three levels (50, 100 and 150% of the level present in the capsule) and the total was measured by the proposed methods. The determination with each amount was repeated three times and the results of this study presented in Table 3 indicated that the various excipients present in the formulations did not interfere in the assay.

CONCLUSIONS

This is the first report on the assay of gabapentin in formulations by titrimetry. The assay results demonstrate that it is possible to determine the GBP in capsules by titration in non-aqueous medium using perchloric acid. In particular, the titrimetry is much simpler in technique, more rapid than all the previous

Table 2. Comparison of assay results of proposed and reference methods (mean value of five determinations)

Capsule brand name	Nominal amount, mg	Found, % (of nominal amount±*SD*)		
		Reference method	Proposed methods	
			Visual method	Potentiometric method
Gabantin-100	100	100.80±0.84	99.65±1.05	101.83±1.19
			t^a = 1.91	t = 1.58
			F^b = 1.56	F = 2.01
Gabapin-300	300	99.91±1.15	98.23±0.78	99.02±1.43
			t = 2.70	t = 1.08
			F = 2.17	F = 1.55

[a]Tabulated t-value at the 95% confidence level is 2.78; [b]tabulated F-value at the 95% confidence level is 6.39

Table 3. Results of recovery study using the standard-addition method

Formulation studied	Visual method				Potentiometric method			
	GBP in capsule, mg	Pure GBP added, mg	Total found mg	Pure GBP recovered[a]±*SD*, %	GBP in capsule, mg	Pure GBP added, mg	Total found mg	Pure BUP H recovered[a]±*SD*, %
Gabantin-100	3.98	2.00	5.95	98.50±2.45	4.07	2.00	6.05	99.00±1.86
	3.98	4.00	7.89	97.75±1.23	4.07	4.00	8.00	98.25±2.02
	3.98	6.00	9.93	99.17±0.86	4.07	6.00	10.10	100.50±1.21
Gabapin-300	5.89	3.00	8.91	100.67±1.63	5.94	3.00	8.99	101.67±2.31
	5. 89	6.00	11.87	99.67±0.74	5.94	6.00	12.07	102.17±1.97
	5. 89	9.00	14.75	98.44±1.08	5.94	9.00	14.90	99.56±1.66

[a]Mean value of three determinations

reported methods so far for the assay of GBP. The proposed methods are applicable over a wide range (1.0-16.0 mg of GBP) and provide very accurate and precise results. Although several instrumental techniques have been reported for the assay of GBP in pharmaceuticals they suffer from such drawbacks such as time consuming, require multistage procedures and require expensive instrumental setup. The wide applicability of the new procedures for routine quality control is well established by the assay of GBP in pure form and in capsules.

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NAUČNI RAD

TITRACIONA ANALIZA GABAPENTINA U KAPSULAMA PRIMENOM PERHLORNE KISELINE KAO TITRANTA U NEVODENOJ SREDINI

Opisane su dve jednostavne, tačne i jeftine titracione metode za određivanje gabapentina (GBP) u rasutom stanju droge, kao i u kapsulama. Metode se zasnivaju na reakciji neutralizacije primarne amino grupe GBP perhlornom kiselinom u glacijalnoj sirćetnoj kiselini. Završne tačke su određene titracijom uz kristal violet kao indikator ili potenciometrijskom titracijom koristeći elektrodni sistem koji se sastoji od modifikovane staklene i ZKE elektrode. Reakcije se odigravaju u stehiometrijskom odnosu 1:1. Obe metode su uspešno primenjene za određivanje GBP u kapsulama u opsegu 1,0-16,0 mg. Validnost predloženih metoda je dodatno potvrđena paralelnim određivanjem referentnom metodom i određivanjem procentnog prinosa (recovery vrednosti) metodom standardnog dodatka.

Ključne reči: ispitivanje gabapentina; titrimetrija; potenciometrija; kapsula.